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COMMENTARY

Reactive oxygen species production by circulating monocytes: insights from pathophysiology to clinical hypertension

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Reactive oxygen species (ROS) are a family of molecules including molecular oxygen and its derivatives produced in all aerobic cells. Increasing evidence indicates that ROS play a pathophysiological role in the development of hypertension.[1,2] This is due, in part, to the promotion of endothelial dysfunction by ROS excess (oxidative stress), where the endothelium plays an integral role in the regulation of vascular tone, platelet activity, leukocyte adhesion and thrombosis.

Endothelial dysfunction is associated with reduced nitric oxide availability.[3] Such disruption of normal vascular endothelial integrity or function permits the capture of circulating monocytes on the endothelium and subsequent diapedesis. Indeed, animal studies indicate that circulating monocytes are precursors to the lipid-laden macrophages within atherosclerotic lesions.[4] In line with atherosclerotic plaque growth and rupture through the elaboration of proinflammatory cytokines and metalloproteinases,[5] ROS may play an intergral role, for example, in activating redox-sensitive signalling pathways, such as the transcription factor: nuclear factor-κ beta.[6]

In this issue of the *Journal of Human Hypertension*, Watanabe *et al*.[7] report a moderate but highly significant relationship between ROS production by circulating monocytes (by flow cytometry) and carotid intima-media thickness (CIMT, as a surrogate of atherosclerosis) among patients with hypertension. These observations are, therefore, consistent with the pathogenesis of atherosclerosis. Based on these data, it is perhaps tempting to speculate that increased ROS production by circulating monocytes may lead to increased oxidative stress within the plaque upon infiltration, with the resultant loss of smooth muscle cells and plaque instability.[8] However, such hypotheses would be premature, as this study – by its very design – cannot establish a cause–effect relationship.

Certainly, it is not clear whether circulating monocytes with increased ROS production are the consequence of some primary vascular damage. Instead, these data from Watanabe *et al*.[7] should prompt further studies into ROS production by circulating monocytes in the broader context of cardiovascular risk (beyond raised arterial blood pressure *per se*), its relationship with the progression of atherosclerotic vascular disease and potential therapeutic implications.

Nonetheless, the enzymatic sources and the aberrant trigger for increased ROS production in circulating monocytes are interesting questions promoted from this research. For example, physiological concentrations of homocysteine have been shown to upregulate the production of ROS in cultured human monocytes, through the action of NAD(P)H oxidase, increasing the expression of key chemokines (e.g. monocyte chemoattractant protein-1 and interleukin-8) which have been mechanistically implemented in the early process of atherosclerosis.[9] Hence, it would be interesting to decipher whether the observations by Watanabe *et al*.[7] are dependent on these homocysteine-induced proatherogenic effects.

How are these observations relevant to clinical practice? Hypertension is frequently associated with other cardiovascular risk factors, most notably, obesity, glucose intolerance or diabetes and dyslipidaemia – this coalition of risk factors is now recognized as the so-called 'metabolic syndrome'.[10] This clinical syndrome is well-recognised to be associated with increased cardiovascular morbidity and mortality.[11] We have previously demonstrated high plasma von Willebrand factor (vWf) levels, an index of endothelial damage/dysfunction in patients with WHO-defined metabolic syndrome, and levels increased in a stepwise fashion with cumulative number of components of this syndrome.[12] Whether ROS production by circulating monocytes increases

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with accumulating cardiovascular risk factors, or indeed with the patient's overall cardiovascular risk remains to be demonstrated. The finding by Watanabe *et al.*[7] of an independent association between HbA1c and monocyte ROS production at least lends support to a potential synergistic interaction between glycaemia and raised arterial blood pressure.

Watanabe *et al.*[7] also imply that assessment of ROS production by circulating monocytes may serve as a useful marker for carotid atherosclerosis. Measurement of ROS production is unlikely to be a substitute for carotid ultrasound imaging, which is a safe, noninvasive, relatively standardised technique, and is supported by a wealth of clinical cross-sectional and prospective data.[13–16] Indeed, carotid intima-medial thickness has recently been suggested to be the most reliable and simplest parameter for predicting hypertensive target organ damage, including microangiopathy, in patients with essential hypertension.[16]

Contemporary guidelines recommend initiation of antihypertensive therapy based on absolute blood pressure measurements in conjunction with estimation of the patients' cardiovascular risk or presence of target organ damage.[17] Some guidelines even suggest that hypertensive 'target organ damage' can be broadened to include additional surrogate indices, such as endothelial dysfunction and carotid intimal-thickness.[18] The enthusiasts would even suggest that estimation of cardiovascular risk may be further refined if the prognostic significance of various indices of vascular biology, such as ROS production by monocytes can be supported by prospective studies. The therapeutic implications of such a link may also be inferred. For example, angiotensin converting enzyme inhibitors, with their demonstrated benefit on vascular function have already been proposed as a treatment for endothelial dysfunction.[19] Clearly, such therapeutic approaches will need further evaluation as is currently underway, for example, with C-reactive protein-guided statin therapy.[20]

In conclusion, oxidative stress is implicated in the pathophysiology of endothelial damage or dysfunction, and atherosclerosis. The study by Watanabe *et al.*[7] amongst hypertensive patients add to these data but still leaves many questions, on the putative link(s) between pathophysiology and clinical relevance, that (sadly) still remain unanswered.

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